Health risks associated with the use of electronic cigarettes - Summary in English

Since electronic cigarettes (e-cigarettes) were introduced to the market, their use has increased steadily, particularly in countries where they are easily available. Data from other countries show that the use of e-cigarettes is growing among the youngest age groups, and that interchangeable use with regular cigarettes is on the rise.

Data from Norway (SIRUS, 2015) indicate that so far it is mainly smokers and former smokers who have both experimented with e-cigarettes and have become regular e-cigarette users. There seems to be no clear gender or educational differences between e-cigarette users and the rest of the population. Adolescent use resembles adult use and is mainly concentrated in groups with previous experience of tobacco.

From the present data (SIRUS 2015), it can be assumed that about 50 000 people use e-cigarettes weekly or more often, 100 000 people use e-cigarettes less frequently, while about 500 000 people have only tried once or a few times. The prevalence of regular use of e-cigarettes was relatively high among people who smoked and among those who had reduced from daily to occasional smoking. Based on the NIPH assessment, these data seem to indicate that e-cigarette smoking in Norway may have served as a means to quit regular smoking and until now has not acted as a gateway to starting tobacco use. The question is whether this will still be the case if e-cigarette use becomes much more commonplace.

There are hundreds of brands of e-cigarettes on the market with thousands of flavours, and the number is increasing dramatically. The market is also unregulated, with extensive trading over the internet. However, it seems that the tobacco industry is becoming increasingly involved in the production, marketing and sale of e-cigarettes. Although we now know something more about the extent of e-cigarette use in Norway, we still know little about which substances users are exposed to because of the wide variety of types of e-cigarettes and content of substances in the e-cigarette liquid. We also know very little about how e-cigarette use in Norway will develop, particularly if they are allowed to be sold in Norway.

As of today, there is insufficient knowledge to make a complete health risk assessment of e-cigarettes as a product. It is also impractical to make a hazard and health risk assessment of all the substances that may be present in the liquid and aerosol from e-cigarettes. Knowledge about many of these substances is lacking or is based on data from occupational exposure to much higher concentrations than are appropriate for e-cigarette use. In this report we have therefore performed health risk assessments of the main individual components of e-cigarette liquid, as well as their potentially more hazardous metabolites. We have also performed an assessment based on direct exposure to aerosols from e-cigarettes, based on the limited data about exposure and health effects that exist.

When the liquid in the e-cigarette is heated and air is drawn over the cartridge, the aerosol of liquid particles that is formed is inhaled. The size and concentration of these particles are comparable with the particles formed from regular cigarettes. The aerosol from the e-cigarettes contains propylene glycol, glycerol, nicotine and a variety of flavourings. Small amounts of tobacco-specific nitrosamines (TSNA), various aldehydes (formaldehyde, acetaldehyde, acrolein), polycyclic aromatic hydrocarbons (PAHs), tobacco alkaloids, volatile organic compounds and various metals have also been detected in aerosols. The particles in the aerosol act as carriers for nicotine and the other inhaled substances and will, depending on the particle size, be deposited in the nasal cavity, oral cavity, the airways (bronchi) or in the air sacs

(alveoli). Where the particles are deposited and their composition can be significant for their effects.

Measurement of the contents of e-cigarette liquids shows very large variation between different products/types. There is also great variation in the measurement methods used and usage patterns (number of puffs, volume, duration etc.). This makes it very difficult to estimate what an e-cigarette user actually inhales.

Aerosol particles are readily soluble and in our assessment will not have any adverse health effects as fluid particles, but only as carriers of the "desired" and "undesirable" substances. Nicotine is the main ingredient in e-cigarettes that contributes to the desired stimulatory effect but is also clearly important with regard to the unwanted, harmful health effects. From measurements of nicotine in the blood of e-cigarette users, we know that an e-cigarette user can inhale as much nicotine as someone who smokes regular cigarettes. Therefore, the same nicotine-related effects of e-cigarette use as from conventional tobacco products must be expected. Nicotine exposure will vary considerably depending on the type of e-cigarettes and usage patterns. However, the user will attempt to ingest the dose of nicotine that gives the desired stimulatory effect.

Nicotine acts primarily via nicotinic acetyl cholinergic receptors found in the nervous system and a number of other organs and tissues such as muscle, lung, blood vessels, brain, kidneys and skin. These receptors activate several cell signaling pathways that are involved in physiological functions, but nicotinic stimulation of these receptors may also cause many of nicotine's unwanted and harmful effects.

Nicotine has a significant addictive potential. We also know that nicotine has acute effects on the cardiovascular system in the form of constriction of small blood vessels, increased heart rate and blood pressure. The long term effects of nicotine exposure are more uncertain and their role in the development of atherosclerosis and acute coronary heart disease is debated. However, there are data which may indicate that nicotine exposure can affect mortality after myocardial infarction. There is therefore reason to warn against the use of e-cigarettes for people who have or have had such a disease. In addition, nicotine can reduce sensitivity to insulin, which may in turn increase the risk of atherosclerosis.

There is reason to believe that nicotine from e-cigarettes plays an important role for adverse effects on reproductive health equivalent to that seen in women who smoke regular cigarettes. Nicotine exposure during pregnancy may inhibit lung development in the foetus and affect pulmonary function in the child in later life. Structural and functional changes in the brain may also occur as a result of nicotine exposure at a young age. Moreover, it is important to be aware that nicotine exposure via e-cigarette use will establish and/or maintain nicotine dependence similar to that observed with conventional tobacco products.

Exposure to carcinogenic TSNAs and nicotine-derived nitrosamine ketones (NNK) as individual substances from e-cigarettes seems to pose a very low risk of cancer development. However, many of these substances damage the cells' genetic material and safe lower limits cannot be set for how much of these substances are required to induce adverse health effects in the body.

A possible risk of cancer associated with exposure to formaldehyde and acetaldehyde from e-cigarette use seems to be very low. Based on animal experimental studies, formaldehyde is considered to have a threshold value for carcinogenic effects. Presumably, this also applies for acetaldehyde which has a similar structure to formaldehyde. It cannot be completely excluded that the most active e-cigarette users with a higher temperature on their e-cigarettes expose

themselves to a slightly increased, but still low, risk of cancer of the nasal cavity / pharynx associated with formaldehyde and acetaldehyde exposure. There is insufficient knowledge concerning this. Formaldehyde and acetaldehyde levels in e-cigarette aerosols probably only cause slight irritation to the eyes and respiratory tract. For acrolein, which does not seem to be carcinogenic, there is evidence that exposure via e-cigarettes may cause irritation in the respiratory tract of users.

Cancer risk from exposure to the measured PAHs in aerosol must be regarded as negligible as the levels are very low. There are two PAHs in aerosol that are classified by the International Agency for Research on Cancer (IARC) as possible carcinogens in animals. Other PAHs in aerosol are considered to be Group 3 substances that are not classifiable with respect to their carcinogenicity.

Cancer risk associated with exposure to nickel or cadmium from e-cigarette use appears to be negligible. If it is assumed that nickel is in the form of oxides (carcinogenic), the levels are still very low and the risk of cancer must be considered to be negligible. The same applies to cadmium. Aerosols from e-cigarettes may also contain lead, which is known to have harmful effects on the nervous system. Current exposure levels seem very low and the risk of effects is negligible. It is unlikely that chromium is in the harmful hexavalent form. Therefore, there is probably no risk of cancer associated with exposure to chromium from e-cigarettes.

Exposure to propylene glycol and glycerol via the respiratory and gastrointestinal tracts is relatively high when using e-cigarettes, but these are quickly excreted from the body. The figures for the levels of propylene glycol in aerosol are spread out, which can be due both to differences in measurement methods, and differences between e-cigarettes and how they are used. When exposed to the highest levels measured, irritation in the airways can be expected. Glycerol exposure will probably not cause irritation.

A myriad of flavourings are added to e-cigarettes, so the knowledge of composition and quantities available are lacking. Many of these substances are presumably not hazardous, both because of little toxic potential and limited exposure. However, it cannot be completely excluded that the flavourings used may include substances that will irritate the mucous membranes of the respiratory tract or have other harmful effects. More knowledge is required.

Some studies of exposure to aerosols from e-cigarettes *per se* suggest that e-cigarettes can contribute to acute irritation and airway inflammation. There have only been a couple of studies about e-cigarette use and possible effects on the cardiovascular system so it is too early to draw conclusions. More detailed studies are needed to verify that nicotine exposure by e-cigarette use causes the same harmful effects on the cardiovascular system as regular cigarettes. The same applies to other effects such as addiction, respiratory function development and reproductive health.

An important question is whether passive smoking from e-cigarettes can lead to the same adverse health effects as regular cigarettes. The present data suggest that nicotine levels in the environment following passive exposure to e-cigarette aerosols causes similarly high nicotine levels in the blood as that of passive smoking of regular cigarettes. This means that one can expect similar harmful nicotine-related effects of passive smoking from e-cigarettes as for regular cigarettes. This does not mean that passive exposure to aerosols from e-cigarettes causes carcinogenic effects, but that passive smoking may affect the cardiovascular system, have stimulatory effects and contribute to addiction. Whether effects on reproductive health or lung development will occur will depend on the degree of exposure. More in-depth studies are needed.

CONCLUSION

Since there are limited studies of exposure to e-cigarettes and adverse health outcomes, the present assessment is almost exclusively based on studies of the individual components of e-cigarettes. There are many different types of e-cigarettes, with varying contents of nicotine and other substances. Both this and different usage patterns could affect health outcome.

The main component of e-cigarettes is nicotine. This applies both to the "desired" stimulatory effect, but also for the "unwanted" adverse health effects that can be expected with e-cigarettes. The intake of nicotine from e-cigarettes seems to be similar to that found with tobacco smoking and snus consumption, indicating that similar nicotine-related effects are expected on the cardiovascular system, lung development in unborn children and in later life, reproductive health (premature birth, stillbirth and preeclampsia) and cognitive effects. It is reasonable to assume that people with existing cardiovascular disease will be more vulnerable to adverse effects on the cardiovascular system (both acute and chronic) than people without heart disease. Furthermore, unborn babies, children and adolescents are considered to be particularly sensitive to nicotine exposure.

Substances such as propyleneglycol and acrolein may cause irritation during e-cigarette use. TSNA, formaldehyde, acetaldehyde, PAH compounds and various metals (nickel, cadmium) are known to contribute to the carcinogenic effect of tobacco smoking. Exposure concentrations to these substances with e-cigarette use are very low and we consider the cancer risk to be negligible. However, this conclusion is based on the separate assessment of the individual substances in aerosols. Further research based on inhalation of aerosols from e-cigarettes is required to verify these conclusions. The effects of long term use of e-cigarettes must be evaluated, particularly in terms of cancer risk, cardiovascular disease and other adverse health outcomes.

From a public health perspective, it is important to prevent new generations from becoming addicted to nicotine, and using e-cigarettes as a gateway to other forms of nicotine such as regular smoking and snus consumption.

For smokers who are unable to quit smoking, it must be assumed that a full transition to e-cigarettes will incur a risk reduction, particularly with regards to cancer development. Until now there have been no independent data that document how smokers as a group switch to e-cigarettes. It is therefore very uncertain to what extent the use of e-cigarettes, combined with regular smoking, will lead to reduced health risks.

It should be emphasized that the use of e-cigarettes alone will still involve a risk of adverse health outcomes among users, particularly associated with the intake of nicotine. The health risks from long-term e-cigarette use in the population is unknown.

Nicotine levels in the environment from passive exposure to aerosols from e-cigarettes can result in similar high nicotine levels in the blood of a passive smoker of regular cigarettes. This means that similar harmful nicotine-related effects can be expected for passive exposure to e-cigarettes as for regular cigarettes. This means that passive exposure to aerosol from e-cigarettes may act on the cardiovascular system, have stimulatory effects and contribute to addiction.